

Significant Improvement in Short-Term Mortality in Women Undergoing Coronary Artery Bypass Surgery (1991 to 2004)

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Objectives	This study sought to evaluate gender differences and trends in 30-day mortality after coronary artery bypass surgery (CABG).
Background	Evidence for gender differences in short-term mortality after CABG is conflicting. Many studies were from single centers, included highly selected populations, or had limited clinical information for adequate covariate adjustment. We undertook a population-based analysis using detailed clinical data on all adults undergoing CABG in the province of British Columbia, Canada.
Methods	The study population comprised all residents 20 years and older who underwent isolated CABG between 1991 and 2004. Multiple logistic regression was used to examine the association between gender and 30-day mortality; time trend analysis was conducted by Mantel-Haenszel chi-square test.
Results	The study cohort comprised 20,229 men and 4,983 women. Women were older and had more comorbid conditions than men, but had better ejection fractions and less extensive coronary disease. Thirty-day mortality decreased significantly in men (2.4% to 1.9%) and women (5.6% to 1.9%) over the 14-year study period. Overall, 30-day mortality was significantly higher in women (3.6% vs. 2.0%, $p < 0.001$), and adjustment for baseline differences did not remove this difference (odds ratio 1.42, 95% confidence interval 1.15 to 1.75). Adjustment for body surface area, an intrinsic gender difference, further attenuated the relationship (odds ratio 1.26, 95% confidence interval 0.96 to 1.64).
Conclusions	The 30-day mortality after CABG decreased significantly between 1991 and 2004, especially in women, suggesting that the gender difference in short-term outcomes is diminishing. The overall 42% higher mortality risk in women seems to be partially mediated through body surface area, a surrogate for vessel size. (J Am Coll Cardiol 2007;49:1552–8) © 2007 by the American College of Cardiology Foundation

Gender differences in mortality after coronary artery bypass surgery (CABG) remain controversial. Resolution of this issue is difficult given that a randomized trial for evaluating gender difference is impossible. Most of the observational studies that have examined gender differences in short-term mortality (in-hospital or 30-day) provide conflicting evidence, with several studies reporting increased mortality in women (1–7), whereas others show equivalent outcomes

(8–12). However, the weight of the evidence indicates that short-term mortality is higher in women than in men. The most recent 2002 data from the Society of Thoracic Surgeons National Cardiac Surgery Database reported an operative mortality of 3.54% in women compared with 2.15% in men (7).

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There are several possible explanations for the inconsistent findings, including selection or referral bias and inadequate adjustment for gender differences in baseline characteristics. Many studies are from single-center tertiary care settings, or they include selected patients (e.g., Medicare patients). Other studies included only minimal information on patient characteristics, limiting the ability to adjust for well-documented differences in baseline characteristics between women and men.

We therefore undertook a population-based study of 30-day mortality in all adults undergoing isolated CABG in the province of British Columbia using detailed, prospectively collected demographic, clinical, and procedural data.

Methods

Population and data sources. All patients undergoing isolated CABG in British Columbia between 1991 and 2004 were eligible for the study. Patients were excluded if they were less than 20 years old or if they were not British Columbia residents. The study cohort was identified from the British Columbia Cardiac Registry, which prospectively captures information on all invasive cardiac procedures performed in British Columbia. All CABG procedures are performed at 4 tertiary care centers. Dedicated personnel enter detailed demographic, procedural, and clinical information on each patient into the Registry database. Fewer than 3% of British Columbia patients undergo CABG outside the province. Deaths within 30 days of surgery were obtained from the British Columbia Vital Statistics Agency Death Registry through probabilistic linkage using patient identifying information, including each patient's unique personal health number. Based on previous work, we know that data linkage between the British Columbia Vital Statistics Agency and the British Columbia Cardiac Registry identifies between 95.7% and 99.8% of deaths (13).

Analyses. Gender differences in baseline characteristics were first examined univariately using Student *t* and chi-square tests, as appropriate. Multiple logistic regression was used to examine the relationship between gender and 30-day mortality adjusting for various covariates. Covariates were selected based on clinical relevance and the significance of univariate associations ($p < 0.2$). All variables were kept in the model if they were clinically relevant or statistically significant ($p < 0.05$). Covariates that were examined included gender, age, year of surgery, acute coronary syndrome (unstable angina/acute myocardial infarction < 6 weeks), prior cardiac surgery, diabetes, heart failure, chronic obstructive pulmonary disease, stroke, renal disease, systemic hypertension, pulmonary hypertension, urgency status, ejection fraction, Canadian Cardiovascular Society angina class, number of diseased vessels, number of bypass grafts, cross-clamp time, arterial graft use, and body surface area (BSA). We also evaluated interactions between gender and age, and gender and BSA. The differential rate of decline in mortality between the genders was examined by evaluating the interaction between gender and surgical years, a test for difference of the linear year trend between genders. Gender differences over time in patient conditions and surgical technique were also examined by logistic regression. The univariate assessment of time trend on 30-day mortality was conducted using the Mantel-Haenszel chi-square test. All statistical analyses were performed using the statistical analysis software

SAS (version 9.1, SAS Institute Inc., Cary, North Carolina).

Results

The study cohort comprised 20,229 men and 4,983 (19.8%) women. Women were on average 3 years older than men, and were more likely to present for emergency surgery and with acute coronary syndrome. Compared with men, women had less extensive coronary disease and better-preserved left ventricular function, as assessed by ejection fraction. The prevalence of stroke, heart failure, systemic hypertension, and diabetes was significantly higher in women than in men. The use of arterial grafts was lower in women irrespective of the extent of vessel disease (Table 1).

Overall 30-day mortality was 2.0% in men and 3.6% in women ($p < 0.001$). At all ages, mortality in women exceeded that in men (Fig. 1) and the greatest difference was

Abbreviations and Acronyms

BSA = body surface area
CABG = coronary artery bypass grafting
CI = confidence interval
OR = odds ratio
RR = risk ratio

Table 1 Baseline Characteristics by Gender

Characteristic	Men (n = 20,229)	Women (n = 4,983)	p Value
Age (mean \pm SD, yrs)	64.2 \pm 9.7	67.1 \pm 9.2	<0.01
Body surface area (mean \pm SD, m ²)	2.0 \pm 0.2	1.8 \pm 0.2	<0.01
Body mass index (mean \pm SD, kg/m ²)	27.9 \pm 4.4	27.9 \pm 5.4	0.90
Extent of coronary disease (%)			<0.01
1- or 2-vessel disease	15.6	19.9	
3-vessel disease	61.0	57.1	
Left main disease	23.4	23.0	
Ejection fraction (%)			<0.01
<35	10.8	8.2	
35–50	33.8	30.9	
>50	55.4	61.0	
Emergency (%)	3.3	4.6	<0.01
Overall arterial grafts used* (%)	80.0	66.9	<0.01
Arterial grafts used by extent of disease* (%)			
1- or 2-vessel disease	78.7	68.0	<0.01
3-vessel disease	80.3	66.3	<0.01
Left main disease	80.5	67.6	<0.01
Off-pump surgery (%)	3.0	3.5	0.11
Acute coronary syndrome	53.9	63.0	<0.01
CCS angina class III or IV (%)	84.3	90.6	<0.01
Prior cardiac surgery (%)	8.7	6.7	<0.01
Stroke (%)	7.6	9.3	<0.01
Heart failure (%)	9.6	12.7	<0.01
Diabetes mellitus (%)	21.5	27.5	<0.01
Peripheral vascular disease (%)	11.4	13.3	<0.01
Renal dysfunction† (%)	11.3	10.6	0.19
Systemic hypertension (%)	42.9	52.0	<0.01
Pulmonary hypertension (%)	3.4	4.1	0.01
Cross-clamp time >1 h (%)	68.0	61.1	<0.01

*Use of at least one arterial graft. †Serum creatinine > 200 μ mol/l or on dialysis.
CCS = Canadian Cardiovascular Society.

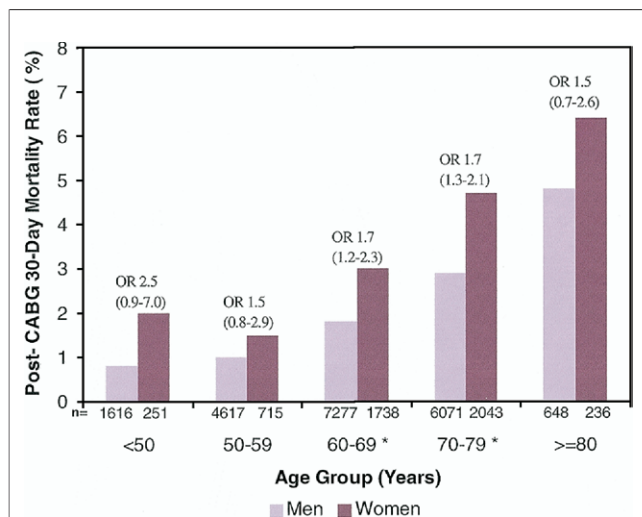


Figure 1 Post-CABG 30-Day Mortality (%) by Gender and Age Group

The odds ratios (OR) shown are the unadjusted ORs for post-coronary artery bypass graft (CABG) 30-day mortality in women compared with men. * $p \leq 0.05$.

observed in the <50-years-old age group (odds ratio [OR] 2.51, 95% confidence interval [CI] 0.89 to 7.09). However, the interaction between gender and age was not statistically significant ($p = 0.74$). Over the 14-year period of the study, 30-day mortality decreased significantly, from 3.1% overall to 1.9% ($p < 0.001$ for trend). The magnitude of the decline among women was the most striking, falling from 5.6% in 1991 to 1.9% in 2004 (Fig. 2).

In the univariate analysis of gender and 30-day mortality, women were 85% more likely to die than men (OR 1.85, 95% CI 1.55 to 2.22). We then developed models in hierarchical order, which we further adjusted for: 1) age, 2)

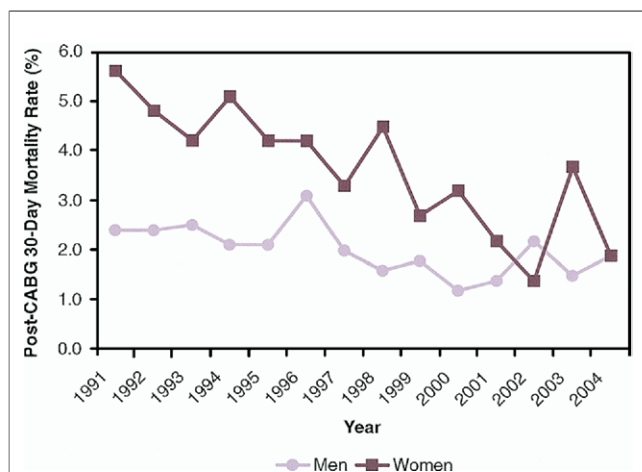


Figure 2 Time Trend for Post-CABG 30-Day Mortality Rate by Gender

CABG = coronary artery bypass graft.

Table 2 Effect of Covariate Adjustments on the Association Between Gender and 30-Day Mortality

Model #	Covariates	Odds Ratio	95% Confidence Interval
1	Gender	1.85	1.55-2.22
2	Model 1 + age	1.64	1.37-1.96
3	Model 2 + comorbid conditions*	1.66	1.35-2.02
4	Model 3 + surgical year + surgical factors†	1.42	1.15-1.75
5	Model 4 + body surface area	1.26	0.96-1.64

*Comorbid conditions were acute coronary syndrome, heart failure, renal disease, diabetes, stroke, ejection fraction, pulmonary hypertension, prior surgery, and urgency status. †Surgical factors were cross-clamp time, off pump (yes/no), arterial graft used (yes/no), and number of bypass grafts.

comorbid conditions, 3) surgical factors and surgical year, and 4) BSA (Table 2). The comorbid conditions included acute coronary syndrome, heart failure, diabetes, stroke, renal disease, pulmonary hypertension, prior cardiac surgery, ejection fraction, urgency status, and number of diseased vessels. The surgical factors included cross-clamp time, off pump indicator, and number of bypasses and arterial graft used. As shown in Table 2, even after adjustment for age, comorbid conditions, and surgical factors, women were still at increased risk compared with men (OR 1.42, 95% CI 1.15 to 1.75). However, after further adjustment for BSA the gender difference was no longer statistically significant. In summary, age adjustment alone accounted for a 21% reduction in risk. Surgical factors and surgical year contributed an additional 24% risk reduction after adjusting for age and comorbid conditions, whereas the addition of BSA resulted in a further risk reduction of 16%. The odds ratio plot for the adjusted model without BSA, model #4 in Table 2, is shown in Figure 3.

The adjusted odds ratio for 30-day mortality by year for women versus men (Fig. 4) illustrates the decline in gender differences after adjustment with model #4. Although year of surgery was significantly associated with 30-day mortality (Fig. 3), the test for interaction between gender and year of surgery did not reach statistical significance ($p = 0.16$).

We also examined BSA, considered a surrogate for vessel size. Small BSA was univariately associated with higher 30-day mortality overall and also when stratified by gender (Fig. 5). However, the association no longer was statistically significant after adjustment for gender and comorbidities, nor was there an interaction between gender and BSA on 30-day mortality ($p = 0.67$). Nevertheless, when BSA was forced into the adjusted model, it attenuated the association between gender and 30-day mortality (OR 1.26, 95% CI 0.96 to 1.64).

To determine whether there were any significant differential changes over time that might explain the steeper decline in mortality in women, we examined several factors for gender differences by surgical year. As shown in Table 3, the gender difference in comorbid conditions did not change over the 14-year time frame, with the exception of BSA, prior cardiac surgery, and renal disease. The gender difference in the number of bypass grafts also did not change over time (p for interaction = 0.31), with women receiving fewer

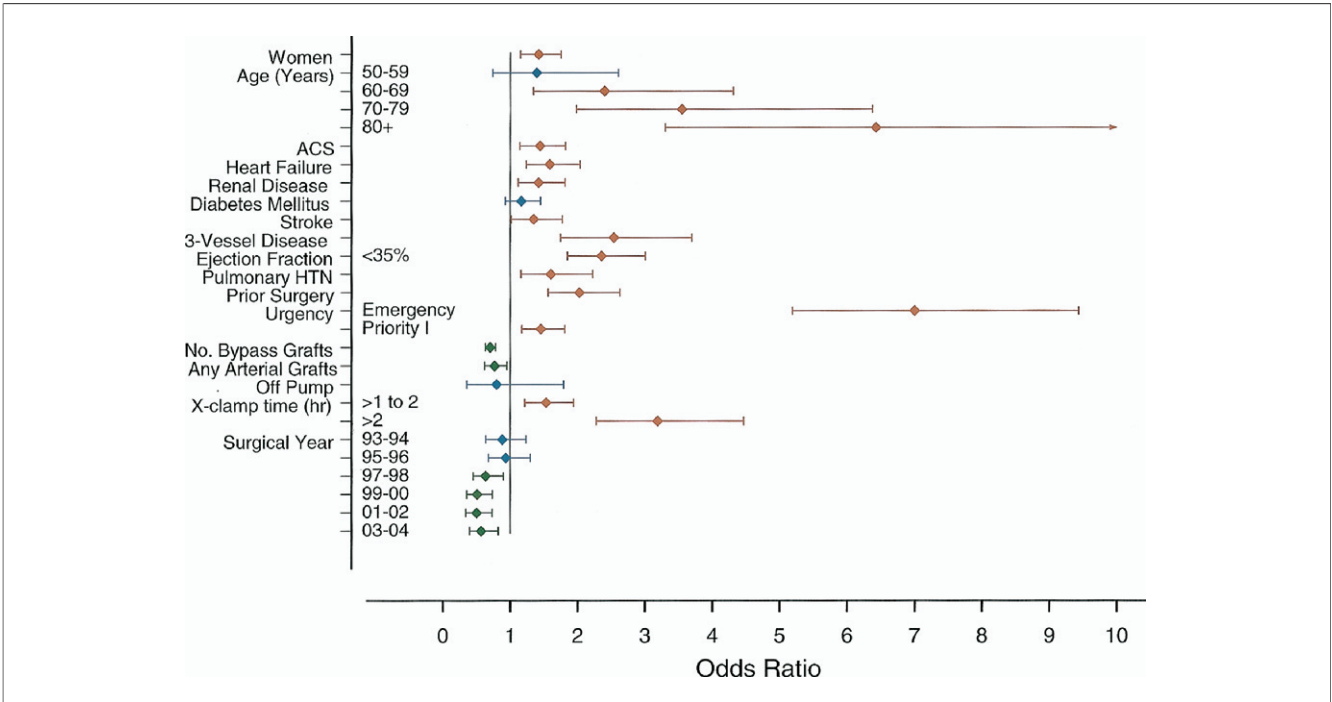


Figure 3 Odds Ratio Plot for 30-Day Mortality (Model #4)

Urgency status levels: Priority I, within 72 h; II, within 6 weeks; III, within 3 months. Reference levels: age <50 years old, 1-vessel or 2-vessel disease, ejection fraction >35%, urgency status Priority II and III, cross (X)-clamp time ≤1 h, surgical years 1991/1992. ACS = acute coronary syndrome; HTN = hypertension.

grafts irrespective of extent of coronary disease (Fig. 6). However, the gender difference in use of arterial grafts changed significantly over time, showing that although women were consistently less likely to receive an arterial graft compared with men, the rate of increase in the use of arterial grafts was greater in women than in men over time

(Table 3). Of note, the lower use of arterial grafts in women was independent of the number of diseased vessels (Table 1).

Discussion

In a population-based study of all adults undergoing isolated CABG in the province of British Columbia, 30-day mortality improved significantly between 1991 and 2004, de-

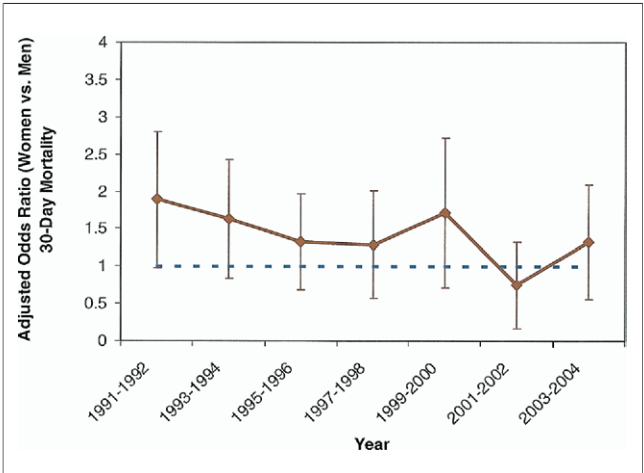


Figure 4 Adjusted Odds Ratios (Women Vs. Men) for 30-Day Mortality by Surgical Year

Odds ratios (women vs. men) and 95% confidence intervals for 30-day mortality are adjusted for age, acute coronary syndrome, heart failure, renal disease, diabetes, stroke, ejection fraction, pulmonary hypertension, prior surgery, urgency status, cross-clamp time, off pump (yes/no), arterial graft used, and number of bypass grafts.

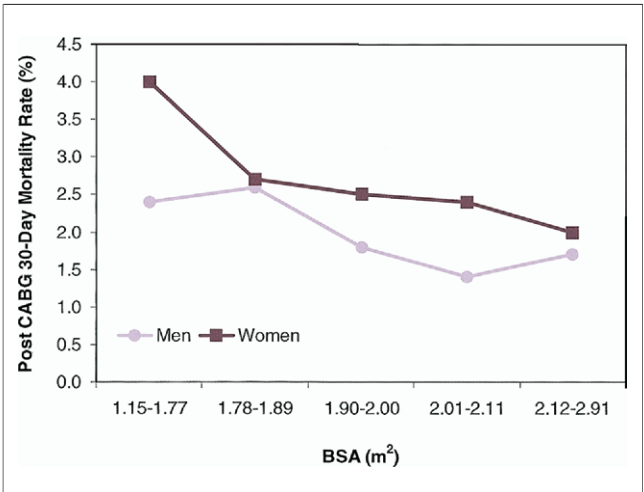
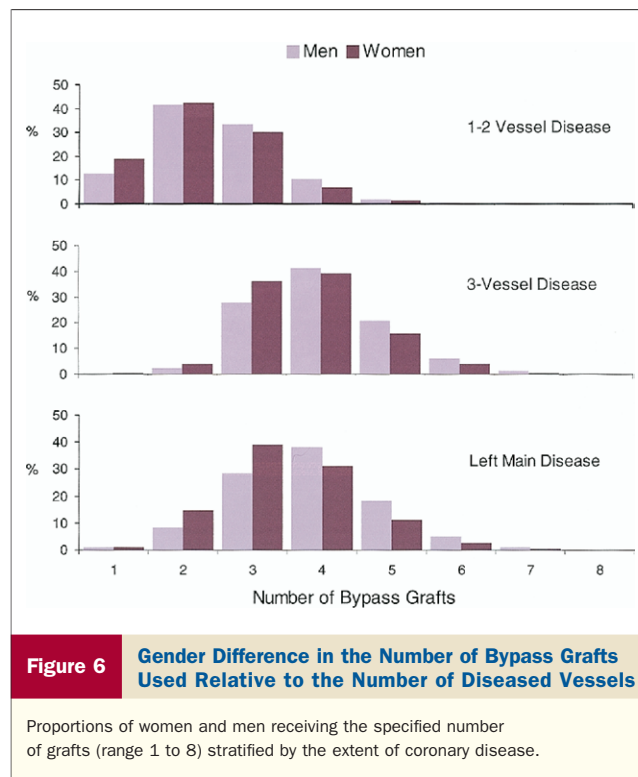


Figure 5 Association Between BSA (in Quintiles) and Mortality by Gender

$BSA (m^2) = ([Height (cm) \cdot Weight (kg)]/3,600)^{1/2}$.
BSA = body surface area; CABG = coronary artery bypass graft.

Table 3 Gender Distribution and Women Versus Men Odds Ratios of Presenting With Selected Baseline Conditions Over Time

Condition	1991-1992	1993-1994	1995-1996	1997-1998	1999-2000	2001-2002	2003-2004	p Value
Women (%)	20.78	20.28	20.91	20.57	19.17	18.57	18.49	<0.001
Odds Ratios of Selected Conditions (Women vs. Men)								
Age ≥ 75 yrs	1.44 (1.12-1.85)	1.89 (1.50-2.38)	1.84 (1.50-2.26)	1.55 (1.27-1.88)	1.71 (1.41-2.07)	1.56 (1.28-1.90)	1.96 (1.63-2.35)	0.39
Body surface area <1.75 m ²	10.23 (8.10-12.91)	12.14 (9.65-15.26)	13.82 (11.15-17.13)	9.74 (7.98-11.89)	10.15 (8.32-12.38)	9.6 (7.83-11.77)	9.14 (7.56-11.06)	0.03
Emergency	1.28 (0.84-1.95)	1.44 (0.99-2.09)	1.32 (0.90-1.94)	1.8 (1.25-2.58)	1.4 (0.88-2.23)	1.08 (0.67-1.74)	1.33 (0.88-2.02)	0.77
3-vessel disease	0.73 (0.59-0.89)	0.91 (0.73-1.15)	0.82 (0.66-1.02)	0.61 (0.50-0.75)	0.67 (0.55-0.82)	0.67 (0.54-0.83)	0.91 (0.73-1.14)	0.86
Ejection fraction $<35\%$	0.9 (0.65-1.24)	0.69 (0.50-0.97)	0.74 (0.55-1.00)	0.75 (0.56-0.99)	0.63 (0.47-0.86)	0.75 (0.55-1.02)	0.74 (0.55-1.00)	0.52
Any arterial graft used	0.44 (0.37-0.53)	0.42 (0.35-0.50)	0.49 (0.42-0.59)	0.55 (0.46-0.66)	0.58 (0.49-0.70)	0.53 (0.43-0.66)	0.55 (0.44-0.69)	<0.01
Cross-clamp time >1 h	0.75 (0.63-0.90)	0.75 (0.62-0.90)	0.8 (0.67-0.95)	0.67 (0.57-0.79)	0.75 (0.63-0.88)	0.7 (0.58-0.85)	0.78 (0.65-0.93)	0.80
Acute coronary syndrome	1.46 (1.23-1.74)	1.78 (1.48-2.14)	1.44 (1.21-1.71)	1.25 (1.06-1.46)	1.43 (1.21-1.68)	1.42 (1.20-1.69)	1.49 (1.27-1.76)	0.50
Prior surgery	0.6 (0.43-0.82)	0.56 (0.39-0.80)	0.74 (0.53-1.02)	0.87 (0.66-1.17)	0.78 (0.57-1.08)	0.8 (0.56-1.15)	0.92 (0.64-1.31)	0.02
Heart failure	1.94 (1.44-2.61)	1.45 (1.08-1.95)	1.04 (0.77-1.40)	1.3 (1.00-1.69)	1.38 (1.09-1.75)	1.43 (1.14-1.80)	1.43 (1.15-1.80)	0.59
Renal disease	0.95 (0.70-1.3)	0.91 (0.65-1.28)	1.35 (1.00-1.82)	1.39 (1.05-1.85)	0.91 (0.71-1.17)	0.83 (0.65-1.04)	0.8 (0.64-1.01)	0.03
Diabetes mellitus	1.61 (1.28-2.03)	1.44 (1.15-1.80)	1.43 (1.16-1.76)	1.37 (1.14-1.64)	1.56 (1.32-1.86)	1.42 (1.19-1.70)	1.27 (1.08-1.51)	0.26
Stroke	1.63 (1.19-2.24)	1.25 (0.90-1.74)	1.4 (1.07-1.85)	1.18 (0.92-1.52)	1.18 (0.88-1.57)	1.01 (0.74-1.39)	1.27 (0.95-1.70)	0.15
Pulmonary hypertension	1.85 (1.04-3.27)	1.11 (0.62-1.98)	0.78 (0.44-1.36)	1.31 (0.85-2.03)	1.12 (0.78-1.60)	1.54 (1.08-2.20)	1.28 (0.89-1.82)	0.71



clining from 3.1% to 1.9% ($p < 0.001$). The mortality rate in women decreased from 5.6% to 1.9% over this time period, but despite this improvement, women were 42% more likely overall to die within 30 days of CABG compared with men. However, after adjustment for BSA, the gender difference was no longer significant (OR 1.26, 95% CI 0.96 to 1.64).

The decline in mortality overall, but especially in women, is noteworthy. The Northern New England group reported similar results after reviewing their data between 1987 and 1997. In the New England study cohort, the absolute decline in the adjusted mortality rate was 3.1% in women compared with 1.5% in men (14). A recent review of CABG in 8 Canadian provinces, using administrative data, also reported significant declines in overall operative mortality, from 3.1% in 1992/1993 to 2.1% in 2000/2001 (2). This study also reported that female gender was associated with a higher risk of in-hospital mortality compared with men between 1992/1993 and 2000/2001, even after adjustment of differences in baseline characteristics.

The observed decline in mortality is unlikely to be caused by temporal changes in either the type of patient undergoing surgery or changes in the distribution of risk factors between women and men. Although there was a statistically significant change in the OR (women vs. men) for renal disease, prior cardiac surgery, and BSA <1.75 , it is important to consider the direction and magnitude of those changes. The changes in renal disease are inconsistent—lower female odds ratio in the earliest period and the latest period—and are thus difficult to interpret. The increase in the female odds ratio for prior cardiac surgery would have increased the

risk of mortality, whereas the decrease in the female odds ratio for BSA <1.75 would favor improved outcome. However, the magnitude of the change in BSA is unlikely to explain the significant decline in mortality that was observed. A possible contributor to the reduction in women's mortality is the increased use of arterial grafts in women over time.

The reasons for the steeper decline in mortality in women remain speculative, but may include improvements in the technique of coronary anastomosis, which would be of particular benefit in patients with small coronary vessels, as well as refinement of perioperative management, which would be expected to provide the greatest benefit to those at highest risk.

Our results with respect to gender differences in 30-day mortality are consistent with those of most studies, which found higher short-term mortality in women (1-7). Another interesting finding was the 2.5-fold higher mortality in women <50 years old compared with men <50 years old. Although this did not reach statistical significance, possibly because of the small number of subjects in this age group, it is consistent with the results from Vaccarino *et al.* (1), in which women <50 years old were 3 times more likely to die in the hospital than men. But our study differs from that of Vaccarino *et al.* (1) because their study included CABG and valve surgery patients, whereas ours included only isolated CABG patients. We examined the characteristics of women <50 years old and found a greater burden of several comorbidities relative to men <50 years old. Younger women had significantly higher prevalence of diabetes, prior myocardial infarction/unstable angina, heart failure, and chronic obstructive pulmonary disease compared with the younger men. These women were also more likely than their male counterparts to undergo emergency surgery, but less likely to receive an arterial graft. Younger women hospitalized with myocardial infarction have also been shown to have higher in-hospital mortality than younger men (1), suggesting that younger women with coronary artery disease may represent a particularly high-risk group.

In the studies that reported no gender differences in outcome, crude rates were higher in women (8-11), but after adjustment for baseline differences, the relative risk dropped from 2- to 1.3-fold and was no longer significantly different from that in men. This is in contrast to our results, in which the gender difference remained significant despite extensive adjustment for baseline differences, including ejection fraction, cross-clamp time, use of an arterial graft, surgical year, and number of bypass grafts. Koch *et al.* (8) performed a propensity-matched analysis in 15,597 patients who underwent isolated CABG and found no gender differences in outcome. It is, however, important to note that 74% of women in that cohort were excluded because they could not be matched, limiting the generalizability of that result.

The importance of BSA, a surrogate for vessel size, on outcomes remains controversial, and the relationship be-

tween gender, body size, and coronary vessel diameter is clearly complex. Gender differences in outcomes have been attributed to small vessel size in women (4,15), and small body size has been shown to be associated with increased operative mortality in some (5,9) but not all studies (16). Mickleborough *et al.* (17) measured the prevalence of small coronary arteries in men and women undergoing CABG and showed that the proportion of women with small (<1.5 mm) coronary arteries (57%) was no different than the proportion of men with small coronary arteries (59%). In contrast, the New England Cardiovascular Disease Study Group reported that even after normalizing for BSA, women had smaller mid-left atrial dimension diameters than men (14). Similar findings were reported by Sheifer *et al.* (18) using intravascular ultrasound to measure arterial and luminal diameters, suggesting that BSA may not adequately reflect coronary artery size.

In the study by Hammar *et al.* (11), adjustment for age and BSA reduced the relative risk (RR) of mortality attributable to gender from 1.8 (95% CI 1.0 to 3.0) to 1.0 (95% CI 0.5 to 2.0). In the analysis by Woods *et al.* (12), even after adjustment with 17 clinical variables, the RR associated with female gender was 1.97 (95% CI 1.21 to 3.19), but with the addition of BSA the RR decreased to a nonsignificant 1.32 (95% CI 0.73 to 2.37). In our study, adjustment for comorbid conditions had little effect on the association, but surgical factors were strong modifiers, even after adjustment for number of diseased vessels and comorbid conditions. The lower number of bypass grafts and the lower use of arterial grafts in women compared with men for the same extent of coronary disease suggests incomplete revascularization in women, which likely impacts both short-term and long-term mortality (19,20).

There are several limitations of this study. Despite the availability of comprehensive clinical information on all patients who underwent CABG, we cannot exclude the possibility that there is residual confounding from unmeasured factors. Among these potential confounders are socioeconomic status and psychosocial profile (21,22), which are known to be differentially distributed by gender and strongly associated with outcome. The failure to show a statistically significant interaction between gender and surgical year on 30-day mortality, despite the impressive improvement in outcomes in women over the 14-year study, is likely attributable to the sample size, specifically the small number of women.

Despite these potential limitations, this study has several strengths. By using all patients undergoing CABG within one province, we have reduced selection bias, but not referral bias, as this relates to who is referred for CABG. Another strength is the 14 years of extensive, prospectively collected clinical information and our ability to reliably capture all deaths, both in and out of hospital, making our follow-up more complete and less selective.

Conclusions

In this large, population-based study, we have shown a higher probability of 30-day mortality in women compared with men after isolated CABG. Adjustment for BSA, an intrinsic gender difference, attenuated the difference in outcome, suggesting that coronary vessel size partially mediates the relationship between gender and outcome. The results of this study also show a significant improvement in overall mortality between 1991 and 2004, with a substantial improvement in women and a consequent narrowing of the gap in outcomes between women and men. Although the improvement in 30-day mortality in women was not statistically different from the improvement in men, a decline from 5.6% to 1.9% is clinically important. Confirmation that the gender difference in outcomes is diminishing should be verified in other contemporary cohorts.

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